P.E.T.Net® Pharmaceuticals, Inc.
Fueling the Power of P.E.T.

June 5, 2002

Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20857

VIA Electronic Submission

RE: Docket No. 99N-4063
Current Good Manufacturing Practice for Positron Emission Tomography Drug Products; Preliminary Draft Proposed Rule [67 **Federal Register** 15344]

Dear Sir/Madam:

PETNet® Pharmaceuticals, Inc. (PETNet) is a nationwide health product company dedicated to positron emission tomography (PET). We operate 30 cyclotron-based PET nuclear pharmacies in more than twenty states, and we are the leading producer of radiopharmaceuticals for PET. We estimate that our MetaTrace® brand of F 18 Fludeoxyglucose (FDG) accounts for almost 60% of the commercially-supplied FDG in use today.

As such, PETNet is affected by the preliminary draft proposed rule, and we are interested in and well qualified to comment on these proposed regulations. PETNet has provided input on the development of PET CGMP's for several years, including participation in the Public Meeting held on May 21, 2002, ("Public Meeting") to discuss the preliminary draft proposed rule.

In general, PETNet supports the preliminary draft proposed rule and is pleased to provide these comments in an effort to assist in its further development.

Organization of the Preliminary Draft Proposed Rule

The preliminary draft proposed rule contains two sections, the first of which is a preamble describing the FDA's position on major topics associated with the proposed CGMP regulations. The second section consists of the proposed CGMP regulations, which the FDA intends to add as a section separate from 21 CFR part 211. The FDA proposes to codify CGMP regulations for PET radiopharmaceuticals as 21 CFR part 212.

Comment

PETNet supports this approach and encourages the FDA to develop CGMP regulations that reflect the unique nature of PET radiopharmaceuticals. We believe the following characteristics define the unique nature of these products:

- *A single vial represents an entire batch of a commercial product.* The single vial (either pharmacy bulk package or multi-dose vial) requires that the QC sample be withdrawn from the same vial used to withdraw individual doses. This results in 100% testing of the product prior to release, as opposed to batch testing performed according to an approved sampling plan.

- *PET radiopharmaceuticals are sterilized by membrane filtration and aseptic transfer into a closed vial.* The aseptic transfers used in the production of PET radiopharmaceuticals are not the same as aseptic processing. Injectable PET products are suitable for human use only after passage through a sterilizing filter and immediate transfer into a sterile vial. This process typically occurs through a needle inserted into a pre-sterilized, pre-assembled, commercially available vial. This differs substantially from typical aseptic processing operations wherein numerous vials and closures are sterilized separately, then the product is filtered into an open vial and the closure then secured in place.
- *The short half-life of positron-emitting radionuclides dictates an ultra-short shelf life for PET radiopharmaceuticals.* The short shelf life inherently provides a reduced risk in the use and distribution of PET products with regard to potential microbial proliferation. In addition, the short half-life limits the geographic distribution of PET radiopharmaceuticals. This requires the production of many daily batches to provide nationwide access to PET radiopharmaceuticals.
- *The delivery of PET radiopharmaceuticals requires a hybrid environment that contains the elements of PET production and the practice of pharmacy/medicine.* We believe the most efficient handling of PET radiopharmaceuticals occurs when production operations coexist with the practice of pharmacy/medicine in the same facility or within very close proximity to each other. In fact, the final step of the production operation (filtration of the product into an empty sterile vial) may occur in the same hot cell that is used to dispense patient-specific doses. The vast majority of commercial PET radiopharmaceuticals will be produced in this environment. Therefore, it is critical that FDA regulation and PET CGMP's accommodate this environment.
- *The high-energy radiation emitted positron-emitting radionuclides requires specially designed equipment for the safe handling of PET radiopharmaceuticals.* The energy of the emitted radiation (511 keV) is higher than that found in other radiopharmaceuticals. The design limitations of shielded devices for the manipulation of PET radiopharmaceuticals must be considered in the development of the PET regulatory framework.

Introduction

Section I of the preliminary draft proposed rule discusses the background of the 1997 FDA Modernization Act (FDAMA) and previous regulations for PET GMP's. The FDA refers to PET GMP requirements published in the September 21, 1999, issue of the **Federal Register** (64 **FR** 51274) as "preliminary draft regulations." Since this Notice, the FDA has conducted further investigations and visited various PET facilities. The result of these efforts is the "preliminary draft proposed rule." After completion of the current review cycle, it appears that the FDA plans to publish a "proposed rule" for comment followed by a "final rule" at a later date. At the Public Meeting, FDA speakers noted that additional public meetings may be held during the future stages of the rulemaking process.

Comment

We believe the FDA should hold additional public meetings and provide adequate comment periods between each stage of the rulemaking process.

We also believe that the FDA should focus on the subject of good manufacturing practices during the research/IND stage of the PET radiopharmaceutical development process. This topic generated extensive discussion during the Public Meeting, but there was insufficient time to deal with it effectively. During the Public Meeting, an FDA panelist noted the possibility of an additional meeting to develop this topic further. We encourage the FDA to organize such a meeting.

Request for Comments on Guidance Document

Section I of the preliminary draft proposed rule requests comments on "whether or not companion guidance documents are a useful accompaniment to the proposed rule."

Comment

In general, we believe guidance documents can be a useful method for dissemination of acceptable embodiments of GMP regulations. We also believe that, as stated by FDA speakers at the Public Meeting, the FDA should provide adequate training for field investigators in order to prevent the perception that the guidance document is a *de facto* regulation. The guidance document must continue to be developed with ample input from the PET community.

Definitions

§ 212.1 of the preliminary draft proposed rule defines the meaning of the technical terms used in the document.

Comment

The preliminary draft proposed rule and the accompanying guidance document seem to interchangeably use the words "small" and "simple" or "large" and "complex" or "few" and "1 or 2." We request clarification of this usage and the inclusion of these definitions in § 212.1, as well as their consistent application throughout the documents.

Further Comments

In addition, we believe that § 212.1 is a critical part of the preliminary draft proposed rule, and we suggest the following modifications:

Active pharmaceutical ingredient. The preliminary draft proposed rule defines "active pharmaceutical ingredient" (API) as a substance that is "intended for incorporation into a finished PET drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the human body, excluding intermediates used in the synthesis of such substance."

We suggest the replacement of API with the term "Active PET Ingredient" and that this term be defined as "A substance that exhibits spontaneous disintegration of unstable nuclei by the emission of positrons in a finished PET radiopharmaceutical that is intended for use in the diagnosis or monitoring of a disease or a manifestation of a disease in humans." This is consistent with 21 CFR part 315.2, which defines "radiopharmaceutical" as "An article that is intended for use in the diagnosis or monitoring of a disease or a manifestation of a disease in humans…"

Batch. The preliminary draft proposed rule defines "batch" as "a specific quantity of PET drug product intended to have uniform character and quality, within specified limits, that is produced according to a single production order during the same cycle of production." The scale of operations, and their typically close proximity to the practice of pharmacy/medicine, at PET production facilities does warrant the use of "production orders." Therefore, we believe this reference is inappropriate and we recommend the "batch" be defined as "a specific quantity of PET radiopharmaceutical intended to have uniform character and quality, within specified limits."

Batch Production and Control Record (Batch Record). The preliminary draft proposed rule lacks a definition for Batch Record. We suggest that a "Batch production and control record (batch record)" be defined as "a unique record that references an accepted Master production record and documents specific details for production, labeling and quality control for a single batch of PET radiopharmaceutical."

Inactive Ingredient. The preliminary draft proposed rule defines "inactive ingredient" as "any intended component of the drug product other than the active pharmaceutical ingredient." We believe usage of the word "component" in this definition is confusing, especially in light of the preliminary draft proposed rule's definition of "component." We suggest the following definition for inactive ingredient: "any intended constituent of the drug product other than the active pharmaceutical ingredient."

PET Center. The preliminary draft proposed rule defines "PET Center" as "a facility that is engaged in the production of a PET drug product." We believe that "PET Center" has historically referred to a facility with both production and scanning capabilities. Therefore, to avoid confusion, we propose that a "PET Production Facility" be defined as "a facility that is engaged in the production of a PET radiopharmaceutical." "PET Center" should be eliminated from the list of definitions.

PET Drug. The preliminary draft proposed rule defines "PET Drug" as a drug that exhibits spontaneous disintegration of unstable nuclei by the emission of positrons and is used for providing dual photon positron emission tomographic diagnostic images. We suggest that the use of the term "drug" is inappropriate and that this definition should be consistent with the definition of an *in vivo* diagnostic radiopharmaceutical, as described in 21 CFR 315. We suggest that a "*PET Radiopharmaceutical*" be defined as "An article that is intended for use in the diagnosis or monitoring of a human disease or a manifestation of disease and that exhibits spontaneous disintegration of unstable nuclei by the emission of positrons and is used for providing dual photon tomographic images."

Receiving Facility. The preliminary draft proposed rule defines "Receiving Facility" as "any PET center, hospital, institution, imaging facility, or other entity, or part of an entity that accepts a PET drug product for human use." Although implied in this definition, we believe the definition of "Receiving Facility" should explicitly include nuclear pharmacies that dispense PET radiopharmaceuticals into patient-specific doses. Therefore, we propose that a "Receiving Facility" be defined as "any hospital, institution, imaging facility, nuclear pharmacy or other entity, or part of an entity, that accepts a PET radiopharmaceutical for human use."

Quality Control Unit. This definition should be modified to reflect other discussions we have included in this letter. We recommend that "quality control unit" be defined as "any person or organizational element, independent from production, designated to oversee the execution of the quality control function."

Validation/Verification, etc. The preliminary draft proposed rule defines validation, verification and also uses phrases like "suitable" and "qualification" to describe equipment and quality control methods. We request clarification of these terms. We believe it is important to develop clear, self-consistent definitions for all forms of validation, qualification and suitability as they apply to the production of PET radiopharmaceuticals. We suggest that the term verification is unnecessarily duplicative and that the FDA adopt the following definitions for PET radiopharmaceuticals:

> *Validation.* The documented act of proving by examination and provision of objective evidence that any procedure, process, equipment, material, activity or system actually and consistently leads to the expected result.
>
> *Process Validation*. Establishing by objective evidence that the integrated system for executing the process consistently produces a product meeting its predetermined specifications. This may be established by documented evidence through appropriate testing that the finished product produced by a specified process meets all release requirements.
>
> *Methods Validation*. Establishes, by laboratory studies employing qualified equipment, that the performance characteristics of the analytical method meet the requirements for the intended application. Validation is not required for compendial methods.
>
> *Prospective Validation.* Establishing by documented evidence that a process, procedure, system, or equipment used in production does what it purports to do based on a pre-planned validation protocol.
>
> *Retrospective Validation.* Establishing the validity of a process for producing a product that is based upon accumulated evidence from production, testing and control batch data.

Installation Qualification (IQ). Documented assurance that the specified equipment was installed to meet the manufacturer's specifications. Equipment and component parts identification, utility requirements,

major component specifications, construction materials, and safety features are all evaluated at this level. The vendor or the user can perform IQ.

Operational Qualification (OQ). Documented assurance that the equipment operates within the manufacturer's specifications in the user environment. The evaluation requires information on the calibration, control functions and general operation of the equipment. For analytical equipment, this includes accuracy, linearity and precision measurements. For process equipment, this includes the operation of sub-systems and/or total system to demonstrate proper operation and calibration.

Performance Qualification (PQ). Documented assurance that the equipment performs the selected application or method correctly. For analytical equipment, tests are performed using standards and validated methodology to ensure reproducibility of results. This includes elements of accuracy, detection limits, quantitation limits, linearity and range. For process equipment, the validated (established) process is executed multiple times (usually three) to ensure reproducibility of the results and to demonstrate that the output (i.e. product) consistently meets predetermined quality criteria.

System Suitability. System suitability tests are applied to chromatographic systems prior to use to verify that the resolution and reproducibility of the chromatographic system are adequate for the analysis to be done. The tests are based on the concept that the equipment, electronics, analyst, and sample constitute an integral system that can be evaluated as such.

Adequate Personnel and Resources

§ 212.10 of the preliminary draft proposed rule discusses adequate personnel and resources used in the production of PET radiopharmaceuticals, stating "What constitutes 'adequate' personnel and resources will depend in part on the size and complexity of the PET drug producer's operations." The draft also states "A PET center having a simple operation that produces only one or two doses each day (or week) of a single PET drug would need fewer personnel…"

Comment

We agree that more complex operations may require more resources. However, we know of very few operations (either commercial or non-commercial) that produce "only one or two doses each day (or week)." Therefore, this statement unrealistically portrays a "simple operation."

A simple commercial operation may be characterized by the production of one or two *batches* each day. It is adequate to employ one or two persons to staff a simple commercial operation. More complex commercial operations may be characterized by the production of three or more batches each day. It is adequate to employ two or more persons to staff more complex commercial operations.

In most cases, the output of a commercial PET production facility is a single vial (either multi-dose vial or bulk pharmaceutical package) that is distributed to a PET pharmacy where the vial is sub-divided into patient-specific doses. In this situation, the number of doses is not a relevant measure of the complexity of the production facility. We suggest that the complexity of a commercial PET production facility be measured by the number of *batches* produced each day instead of the number of *doses*.

In addition, physician referral patterns for PET products may be sporadic. It is possible that a facility may produce several batches of product on one day, and a single batch on another. In this situation, the same facility could have a single person responsible for all production and quality control activities on one day, and more extensive staffing on another. We suggest a flexible framework that allows a facility to be considered "simple" one day and "complex" another.

Quality Control System

§ 212.20 of the preliminary draft proposed rule discusses the quality control system used in the production of PET radiopharmaceuticals.

Comment

We agree with the preliminary draft proposed rule that (a) quality control systems play a critical role in the production process and (b) the regulatory burden of the quality control system should be consistent with the complexity of the operation.

§ 212.20(a) notes that "a quality control unit…has the responsibility and authority to oversee production operations. We agree with this statement, but believe that the CGMP regulations should more clearly differentiate between the *oversight* of quality functions and the *execution* of quality functions. Quality oversight may include approval of specifications, methods, processes and procedures. It is possible to provide oversight with resources located outside the commercial PET production facility. For example, facilities may use consultants to provide oversight, or may rely on a corporate QA/QC department. We believe that the "quality control unit" pertains only to the oversight of the quality function. Regardless of the size or complexity of a commercial PET production facility, the oversight of the quality function should be a separate organizational element from the production element. The execution of quality functions in commercial PET production facilities must be the responsibility of personnel located at the facility. Some examples of these functions include acceptance/rejection of components, approval of final product labeling and the final product release of PET radiopharmaceuticals. Regardless of the size or complexity of the PET production facility, it should be possible for production personnel to execute quality functions.

Components, Containers and Closures

In § 212.40, the preliminary draft proposed rule refers to "components, containers and closures" to describe materials used in the production of PET radiopharmaceuticals.

Comment

We believe the application of this nomenclature to the production of PET radiopharmaceuticals inaccurately reflects the nature of PET production methodologies. This nomenclature has its roots in pharmaceutical processes where a liquid drug product is added to an empty container, the container is sealed with a closure and the assembled unit subjected to further processing as necessary. This situation differs significantly from the preparation of commercial PET radiopharmaceuticals, where the product is aseptically transferred into a single, commercially-available, pre-assembled vial that is used as the container for the final product. We suggest removal of the phrase "container and closure" throughout the preliminary draft proposed rule and use of the phrase "final product container" to describe the pre-assembled, empty vial. In the future, it may be necessary to modify this nomenclature to accommodate changes in PET production technology.

Control of Components and Final Product Containers

Section II.G. of the preamble and § 212.40(c)(1) of the preliminary draft proposed rule discuss specific identity tests. The preamble states "To identify mannose triflate, a PET center could use infrared spectroscopy or nuclear magnetic spectroscopy."

Comment

We believe adequate control in the routine acceptance of components can be achieved without specific identity tests (e.g., mass spectrometry, infrared spectroscopy, or nuclear magnetic resonance spectrometry). In fact, we believe that the use of specific identity tests places a burden on commercial PET production facilities without added control in the quality of the raw material. Instead, we suggest the following controls for incoming components that yield an active PET ingredient:

a. Examination of a certificate of analysis[‡] for the incoming component and comparison to pre-determined specifications
b. When possible, performance of a non-specific identity test (e.g., an accurate melting point determination for mannose triflate)
c. 100% testing of the final product (i.e., [^{18}F]FDG from mannose triflate) prior to release.

[‡]The COA should be signed by the supplier, and should include the results of specific identity tests.

Of course, the actual controls for incoming components should be described by the sponsor in a new drug application.

Master/Batch Production and Control Records

§§ 212.50(b) and (c) describe the requirements for Master and Batch Production and Control Records. These sections seem to describe a detailed Master Production Record and a simpler Batch Record that is a subset of the Master Record.

§ 212.50(b)(2) refers to the parameters that must be included in the master production and control record and refers to the "name and weight…" of each active pharmaceutical ingredient.

Comment

We request clarification on §§ 212.50(b) and (c). We request that the FDA consider the possibility that a Master Record provide a complete description of the PET production process, while the Batch Record provide only the information required for a documented history of the Batch in question. In this way, the Master Record, which may be 10 pages or more, is a descriptive tool and the Batch Record, which may be 3 pages or less, is a documentation tool. We believe this approach simultaneously offers appropriate controls for the commercial production of PET radiopharmaceuticals while minimizing large amounts of paperwork generated from the production of numerous daily batches.[†]

We believe that, with appropriate interpretation (e.g., in the draft guidance document), the only change to accomplish this would be in § 212.50(c)(2), which should read "Each major production step (obtained from the approved master production record)."

Additional Comment

"Weight" is an inappropriate unit of measure for radiopharmaceuticals, which are typically measured in mCi, Ci, MBq, or GBq. The use of weight as a unit of measure should be removed from § 212.50(b)(2) and all other sections.

Radiochemical Yield of PET Radiopharmaceuticals

§ 212.50(b)(6) refers to action limits on the radiochemical yield of a PET drug product.

Comment

The preliminary draft proposed rule implies that the radiochemical yield must be performed prior to product release. Please clarify if this is the case. If the determination of radiochemical yield is a pre-release criteria, then it is important to note that this is not possible for some PET radiopharmaceuticals. In order to determine the radiochemical yield for a PET radiopharmaceutical, one must determine the amount of incoming radioactivity. For example, in the production of [^{18}F]FDG, the amount of incoming [^{18}F]fluoride ion (in mCi, MBq, etc.) must be determined prior to starting the synthesis (this is readily achievable). However, in cases where the radioactive starting material is a gas (e.g., [^{15}O]oxygen, [^{11}C]carbon dioxide or [^{18}F]fluorine gas), it is not possible to measure the incoming radioactivity, and consequently not possible to determine the radiochemical yield of the production process prior to product release.

Retrospective Validation

The preamble to § 212.50(f) discusses retrospective validation states "validation of that production process may be conducted retrospectively provided that the process has not changed and has not resulted in process-related failures."

[†]PETNet estimates that our current nationwide production output of MetaTrace FDG® is more than 60 batches/day. We are therefore very concerned about paperwork requirements associated with Master/Batch Production Records.

Comment

We believe this section is inconsistent with the draft guidance document (lines 1033 through 1041), which states "For a PET center that has an established history of PET drug production, validation of the production processes can be conducted retrospectively, provided that the current process is supported by adequate accumulated data to support a conclusion that the process is normally sufficiently capable of yielding batches meeting predetermined specifications." We request that the preamble be changed to reflect the guidance document.

Laboratory Requirements

§ 212.60 discusses the laboratory requirements used for testing purposes.

Comment

We believe this section inaccurately reflects the relationship between the QC and production functions used in the preparation of PET radiopharmaceuticals. In the vast majority of cases, these areas are located within the same room, but this section implies otherwise. For example, § 212.60(g)(1) describes test records as if the laboratory handles numerous different samples with little or no knowledge of the origin of the sample. This is an inaccurate description of the relationship between QC and production in the PET environment, where the analyst has a detailed understanding of the source of the sample.

We suggest that the following information is sufficient for the test records used for a PET radiopharmaceutical (e.g., by gas chromatography). A print-out of the chromatogram with the calculated amounts of each component analyzed by the test, the date the test was performed, the procedure used to perform the test, the batch identification number of the PET radiopharmaceutical, a statement of how the results compare with established acceptance criteria (i.e., pass/fail), and the initials of the analyst. This information may be directly recorded on, or attached to, the batch record.

Conditional Release Testing

The preamble to § 212.70 of the preliminary draft proposed rule requests comments on several questions related to conditional release of PET radiopharmaceuticals in the event of an unanticipated analytical equipment failure. Each question posed by the FDA is addressed below:

How frequently do breakdowns of analytical testing equipment occur?

The most common analytical equipment used in commercial PET production facilities includes gas chromatography (GC), high performance liquid chromatography (HPLC), and radio-thin layer chromatography (TLC). Generally this equipment is highly reliable, but breakdowns occasionally occur, even with properly maintained equipment.

What is the likelihood that an alternative testing method would be available?

Generally speaking, only thin-layer chromatography is amenable to alternative testing methods.

If a PET drug product could not be released for administration to patients because laboratory testing could not be completed due to equipment failure, what is the likelihood that a different PET center could provide the appropriate PET drug product for these patients?

Dose coverage may be available from other PET production facilities, but this scenario cannot be generalized and is highly situation specific. Regardless, we do not believe this possibility is relevant to the issue. The decision whether or not to institute conditional release provisions should be based on the fact that (a) the testing of PET products requires sophisticated, well-maintained analytical equipment that might fail, and (b) the time critical production environment of PET radiopharmaceuticals may not allow repair of this equipment in time to release the product.

Should there be a specific regulation permitting final release of a PET drug product even though testing cannot be completed due to a failure of equipment?

We believe the FDA should develop specific regulations that would allow the final release of PET radiopharmaceuticals even though certain routine quality control testing cannot be completed due to an unanticipated failure of analytical equipment.

If so, what conditions for release should be established to limit potential risk to patients and ensure that such release does not become standard practice?

We suggest the following conditions for final release when an unanticipated analytical equipment failure occurs:

a. There were no test failures or negative trends concerning the pertinent quality parameter for the previous 20 batches.
b. The radiochemical yield of the batch(es) in question is acceptable according to predetermined action limits.
c. There were no potentially relevant events in the radiochemical process that require a written deviation report.
d. All other quality control results are within specified limits.
e. A reserve sample of the affected batch is retained and tested, if appropriate, when the analytical equipment has been repaired.
f. If radiochemical identity/purity test(s) on the active PET ingredient cannot be performed, conditional release of the final PET radiopharmaceutical is not appropriate.
g. The affected analytical equipment will be repaired in a timely fashion.

Should the receiving facility be notified of the information that is unavailable because of the equipment failure?

We believe that the receiving facility, as defined elsewhere in this letter, should not be notified that a product has been conditionally released. If subsequent testing of the reserve sample reveals that the product is out-of-specification, then an OOS investigation should ensue, and, if the product is found to have failed the test, then the receiving facility should be notified.

Final Product Release Criteria

§ 212.70(c) describes the conformance specifications for PET drug products and requires the testing of each batch "to ensure that the product conforms to specifications, except for sterility, before final release."

Comment

Approved NDA #20-306 for [^{18}F]FDG provides for final product release prior to completion of the test for bacterial endotoxins. In this NDA, the 60-minute test for bacterial endotoxins must be started, but does not have to be complete, at the time of product release. Therefore, we suggest this section be changed to allow this provision. This provision is consistent with monograph for [^{18}F]FDG in the European Pharmacopeia, Third Edition, which states "The injection may be released for use before completion of the test [for bacterial endotoxin]." Finally this provision is consistent with Chapter 125, *Radiopharmaceutical Preparations* in the European Pharmacopeia, Third Edition, which states "It is sometimes difficult to carry out [bacterial endotoxin tests] before releasing the batch for use when the half-life of the radionuclide in the preparation is short. The test then constitutes a control of the quality of production."

In addition, we believe § 212.70 should contain instructions for the investigation of out-of-specification (OOS) results.

Batch QC Failures

§ 212.71 describes actions to take in the event that a batch of a PET radiopharmaceutical fail to meet final product specifications.

Comment

We suggest that § 212.71(a) be changed to read: "You must reject a batch of a PET drug product that does not conform to specifications. You must identify and segregate the product to avoid mix-ups."

Distribution

§ 212.90 describes the control of the distribution process for PET radiopharmaceuticals.

Comment

As we discussed earlier in this letter, the vast majority of commercial PET radiopharmaceuticals will be produced in a hybrid environment where production operations coexist with the practice of pharmacy in the same facility or within very close proximity to each other. This section requires no change as long as it is recognized in §212.90(b)(1) that the receiving facility may be a pharmacy within the same facility as the production operation.

FDA Field Investigators

Numerous times during the Public Meeting, FDA panelists referred to the training of FDA Field Investigators. The panelists noted that a core group of Field Investigators will be specifically trained to inspect PET radiopharmaceutical producers. To prevent the guidance document from becoming a *de facto* regulation, the panelists also noted that Investigators will not be allowed to bring this document to an inspection. In addition, Investigators will be trained to exercise regulatory discretion and to insure this, written observations will be sent to the Office of Compliance to verify the validity of the observations.

Comment

We support this approach to training a core group of Field Investigators and encourage the FDA to adopt the inspection framework discussed in the Public Meeting.

Sincerely,

Steve Zigler

Steve Zigler, Ph.D.
Director, Quality and Regulatory Affairs